C. MENDEL's LEGACY

Omnis cyclus e cosmo: Mendel's chronoastrobiological legacy for transdisciplinary science in personalized health care

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Support: U.S. National Institutes of Health (GM-13981) (FH);

University of Minnesota Supercomputing Institute (GC, FH)

Dedication and Preamble

This presentation, a follow-up on an earlier paper by the senior author (1), is dedicated with infinite gratitude to the memory of his father, Dr. Julius Halberg, who had guided his poetically inclined son to science, medical school, and life in the USA. In the USA, his path led to research into cyclicities in biological and other temporal variability. Chronomes -- time structures -- complement genetic and cosmo-spatial diversity near and far, a first major link to genomics and then to Johann Gregor Mendel, recognized earlier as a geneticist, meteorologist and epidemiologist, all in one person, who pursued these superficially diverse activities during a productive if relatively short lifetime. From the relation of the fields of spatial and temporal variability, the senior author's lifetime concerns, common reciprocal structures emerged in and around us, in whatever was measured. A self-sustaining multifrequency rhythmic pattern of variability was mapped. It organized chaos and underwent trends, while intermodulating, self-reproducing and evolving. Rhythms turned out to be much more than the signature of the cycles in our cosmos, which they are. They also constitute the mechanism of living matter and eventually led to the spirituality of life. As we learn more and more about our chronomes, Figure 1, we recognize them as a product of our cosmoi: chronomes are interwoven but resolvable as somewhat wobbly recurrent patterns. Thus, we gained a perspective of an open system from the perspectives of a chronomedicine, chronoecology and, eventually, a yet broader chronoastrobiology, all transdisciplinarily dependent upon chronomics, the aligned study of biospheric and cosmic time structures, that, while of interest in their own right, complement genomics.

Whatever one measures or renders measurable, repeatedly, densely and/or along longer and longer time scales characterizing individuals, populations and eventually species, genera and their habitats, gains from a resolution of cycles, defined as an inferentially statistically documented recurrent phenomenon in a spectrum consisting of photic and other constituents. For each component cycle, 1. the no-cycle (zero-amplitude) assumption is to be rejected and 2. point-and-interval estimates of parameters are to be provided. Photic variations, notably about (~) 24-hour cycles, are usually environmentally well synchronized, more than the non-stationary, aeolian non-

photics. Based on the foregoing criteria, non-photics and photics both qualify as cycles, until they become rhythms, once they are replicated over many cycles and documented as to intermodulations and their mechanisms. We are dealing with exophased endocycling: many built-in periods in the biosphere can be exogenously synchronized and phase-shifted (whereby we account for the "exophasing") while they persist in the absence of the external cycles, being partly endogenous, the point we are trying to make by "endocycling".

Endeavors in science dealing more broadly with civilization and in particular with a hard-to-define culture are best referred to their temporal as well as to spatial coordinates, and are thus rendered more meaningful in the context of chronomes in us and around us, as Mendel put it, in the context of "terrestrial and cosmic factors". The systematic mapping of the spatial environment has been done by physicists for centuries on earth and for decades via satellites in space: it awaits complementary systematic temporal mapping, in physics and in the biosphere. Mendel, the meteorologist at heart, concomitantly mapped physical conditions and diseases, first with the head of a hospital in Brno, and continued recording them after the latter's death, implementing meteorology in relation to the epidemiology of disease. Mendel the meteorologist practicing chronomics was the topic of a lecture delivered at a symposium held at the Mendelianum in Brno, Czech Republic, here summarized with an update, and was also the topic of a keynote opening a symposium given in Nagoya, Japan, published in 1991, with 70 figures (2). Many more figures mapped in the interim are mostly available at least as bibliographic references, on our website (http://www.msi.umn.edu/-halberg/). The present paper continues to summarize chronomics in the framework of a long-standing cooperation between Brnoese and Minnesotan co-investigators.

Abstract

This paper reviews the development of chronobiology, the science (logos) of life (bios) in time (chronos), and of chronomics, against the background of Mendel's contributions far beyond genetics. In keeping with Mendel the meteorologist, we document for rhythms that light and food are not the only external switches. The "master switch", light, can be overridden more often and more critically than we visualize by feeding (3) or by a magnetic storm (4). Very important

hypothalamic "oscillators" (5) are not the only internal mechanism of rhythms. Time structures, chronomes, reside in every biological unit, pro- or eukaryote, Figure 2 (6; cf. 5, 7). Chronomes in us have a strong genetic component which, in turn, entered the genome in response to environmental chronomes, explored meteorologically by Mendel. The more remote environmental origin of rhythms and their less remote genetic aspect both qualify biological chronomes as the legacy of Mendel the meteorologist as well as the geneticist.

Our continued resonance with the environment renders an exophased endocycling even more interesting. The need for coordinated physical and biological monitoring, the topic of a project on The BIOsphere and the COSmos, briefly BIOCOS, to complement genomics, can also be viewed as the legacy of Mendel the meteorologist/cartographer. Some of Mendel's meteorological data were meta-chrono-analyzed. Mendel himself published more often on meteorology than on what became genetics. His legacies of paraphernalia are those of a meteorologist. Despite failing his examination for certification as a regular teacher in 1850 -- his lowest marks were in biology and geology (!) -- and although he reportedly never passed his teacher's license examination, Mendel started the science that distinguished the rules of dominant vs. recessive behavior and eventually led to the cloning of organisms and the debate about stem cells, again raising the question "What is life?" (1, 8, 9). Mendel is the de facto teacher par excellence of this generation of genomics, proteomics and nanochemistry by virtue of what became not only genetics but also chronomics in Brno. Our advocacy of education in instrumented self-help for chronobiologic literacy includes genetics and ecology, and qualifies as Mendelian. Chronobiologic literacy in everyday health care serves for the quantification of normalcy. By resolving chronomes in the normal range, we act positively rather than defining health negatively and only qualitatively (as the absence of disease, i.e., of deviations outside that range) summarized as % morbidity and % mortality only for a population, not for the individual.

From these several viewpoints that have as a common denominator focus upon the usual, we view Johann Gregor Mendel as a chronobiologist. We view chronobiology in a broad perspective of its now thoroughly documented roots in our genes and via our genome in the cosmoi, as they

were when and where life began and as they changed from then to now. Evolution, ecology, genetics and chemistry, the legacies of Darwin, Haeckel, Mendel and Lavoisier respectively, and their transdisciplinary fusion by Brückner, Egeson, Norman Lockyer, W.J.S. Lockyer, Chizhevsky and Vernadsky in the spirit of Dokuchaev, like everything else, occur in time. They are part and parcel of chronobiology and of a much broader temporal perspective from chronomics, an overdue transdisciplinary cartography of the as-yet unknown.

Omnia metire quaecumque licet, et immensa ad mensuram tempestive et ergo significative redige: Measure what is measurable and render measurable, *meaningfully in time,* what as yet is not

A concern for measurement, revealing variability, led to basic and applied lessons in a broad science, chronobiology, which explores our origins in the cosmoi and offers applications in preventive as well as curative aspects of health and environmental care (10). Chronobiologic concerns, basic or applied, require a dynamic perspective of life and the cosmoi. The need for such a concern about the changes around us as well as in us was fully envisioned by Mendel's activities. His signature impacts far beyond the pea patch of the monastery in Brno, where genetics was born. There, Mendel read Darwin and made notes in the latter's book. He eventually added genetics to natural selection and was concerned, in the struggle for survival, about the "dawn of empathy", about going beyond life as a food chain to lay the basis for fields in which genetically coded life could evolve toward spirituality, which as yet may have escaped classification by otherwise meritorious approaches of physicists and biologists alike (11).

Mendel, the chronobiologist, recorded physical cycles in nature, some of them now shown to be anchored in our genes. In his pre-satellite era, changes in solar wind speed escaped him, but he collected original data on wind speed, meta-analyzed by us to emphasize Mendel's concern about environmental effects, rather than merely to quantify another circannual pattern. Unfortunately, this to-us available series of measurements is not long enough to examine the putative presence of a transyear of ~1.3-years length, non-photic and unseen, and its possible beating with a calendar-yearly component. Transyears characterize our physiology from human babies and the elderly in particular. The ~yearly and ~daily patterns in us and around us, and their importance have become

obvious (12, 13). Much less conspicuous are about half-weekly (circasemiseptan) and about-weekly (circaseptan) changes, unseen, non-photic, in our environment, well known in human pathology since antiquity and now found to have counterparts in helio- and geomagnetic phenomena, as well as in rainfall, where a physical near-match was reported (14). Heliogeomagnetics also exhibit ~half-yearly (circasemiannual), ~10-yearly (circadecadal or circadecennian), ~21-yearly (circadidecadal or circavigintunennian), and other natural, e.g., transtridecadal (15-17; cf. 18) physical cycles and even broader time structures, chronomes, Figure 1, that have biological counterparts and enlarge the scope of biological time measurement, leading us to the essence and origins of life, the feedsidewards, at various levels of organization, Figure 3.

From dense and long time series and inferential statistical procedures applied thereto, we learn that most if not all of the above mentioned and other bioperiodicities resonate with terrestrial and more remote magnetic and/or other solar or galactic activity, a broad field in its own right explored largely without concern for time structures (19). Solar and, perhaps, more remote astral dynamics (recorded by space-borne vehicles, traceably gauged by velocity, proton density and temperature changes in the solar wind) and some of their consequences, include associations with biota. Modern technology complements the tools available in Mendel's time, to build on his legacy and to examine the relative importance of factors in us vs. those around us in determining our "behavior" in the broadest possible sense, including the spheres of the mind (= noos) -- the noosphere -- and of spirituality, the soul, that some researches based on spirituality, located in the pineal, and others in the gut, insofar as melatonin's circadian rise in the intestine, can precede those in plasma, the hypothalamus and the pineal (20).

It took the last quarter-century to explore molecularly the genetics of the ~daily rhythms. Their built-in nature was one reason for coining the various circa-rhythms, "about" (= circa) referring to a frequency characteristic of the biological system approximating an environmental periodicity, yet deviating from precisely that length. Other important considerations for "circa" are being accepted more slowly. One of them is the fact that we are dealing with uncertainties, i.e., with statistical rather than purely deterministic entities. To determine their variability and, once

this is done, to quantify their characteristics, we need inferential statistical procedures for both the testing of a cycle's occurrence and for determining the interval as well as point estimates of its parameters, e.g., as 95% confidence intervals.

Some of the uncertainties encountered reflect the operation of unknown distant as well as of proximal measurable drummers. Cases in point are subtle geophysical associations with myocardial infarctions (21) relating, in their turn, to events from interplanetary space and to Horrebow-Schwabe's ~0.5-year, Hale's ~21-year and Brückner, Egeson and Lockyer's ~35-year cycles (15-18) in solar activity that in turn may be subject to galactic influences. There may also be effects on biota from outside our galaxy, within our cosmos and/or other cosmoi (19). These as yet must be documented.

A hint of possible extra-solar system effects could be provided by any finding in physiology consistently preceding events in solar or interplanetary physics, such as a southward turn of the north-south component, B_z, of the interplanetary magnetic field (IMF). Thereby, the question is raised whether an extra-solar-system factor influences both the IMF and human physiology. Furthermore, an explanation for ~10-year cycles in microbial sectoring, i.e., as probable genetic changes of air bacteria, that are in near-antiphase with the solar activity cycle of similar length, is the possibility that the effect upon the human heart, whether it occurs during a magnetic storm in the laboratory (4) or on the neonatal intensive care unit along the scale of a day or with an ~10-year solar cycle (22) may be an effect of the displacement by geomagnetic storms of the flux of galactic cosmic rays and thus the mutagenic effect of a driver from our own galaxy or from another.

Chronomes and Mendel

By objectively and consistently measuring meteorological as well as biological variation patterns with time and by seeking reproducible patterns in what others may have regarded as random variation, and in particular by interpreting them contrary to the dogma of his era, Gregor Mendel was a scholar not only in chronobiology but also in chronomics: he recorded samples as well as publishing terrestrial weather reports. Meteorological observations from 1856 on were

incorporated by 1862 into publications of the observations of all meteorological stations in Moravia. From 1878 to 1883, Mendel ran a weather station in Brno. In the spirit of Mendel, we are led beyond the molecular genetics of a time-invariant genome to its expression in chronomes. We here draw and test generalizing inferences concerning structures in time. In the chronomes of organisms, the major element, the circa-rhythms, are integrated from within on the one hand, while they are also adapted to external chronomes, including cyclic among other (environmental) patterns, with the perspective broadening from an impenetrable normal range, over clocks and calendars to chronomes, Figure 4.

In its turn, the spectrum of rhythms renders chaotic-appearing changes predictable and diagnostically useful (23, 24) while on the basic side it may point to sites of life's origins by the behavior of rhythms in our ontogeny and phylogeny (25). An example is the prominent biological week found early in human life (26, 27) and again in the human elderly (28). These patterns during aging may "recapitulate" phylogeny and perhaps also those temporal features of cosmogeny, including some prevailing in times long past, when life started on earth and/or beyond in our cosmos and/or in other cosmoi. Data on hundreds of human babies from different geographical areas are pertinent as to ontogeny, as is evidence on dozens of unicells and more limited data obtained early in the ontogeny of the crayfish (29), rats (30) and piglet (31).

The value of chronomes of blood pressure and heart rate variability, apart from their basic interest, relates to self-help for health care, based on a chronobiologic literacy. Too much blood pressure and too little heart rate variability serve in diagnosing an elevation of disease risk, prior to overt illness. The task of detecting Vascular Variability Disorders (VVDs) and their combinations in disease risk syndromes prompts the need for every-man, -woman and -child to benefit from general education in chronobiology. This bioscience complements, by rendering more interesting and more useful, the learning of other sciences such as mathematics, physics and chemistry. Topics in hard science can all be taught by chronomedical examples for self-help in health care, in the spirit of Mendel the teacher who was recognized as such only after his death; Mendel the researcher, who was recognized as the father of genetics only decades after his death; and Mendel

the chronobiologist, whom we recognize as such well over a century after his death. Unlike single sample-based time-unqualified homeostatic biology, which can be misleading, chronobiology renders the teaching of the hard sciences interesting and useful in health and environmental care (32). To be specific, the teaching of the blood pressure measurement certainly is of homeostatic interest, but as such misleading if decisions are based on single measurements or single 24-hour profiles. It is critical to learn in middle or preferably in elementary school that taking a single time-unqualified measurement, from a biomedical viewpoint, can be equivalent in some patients to flipping a coin (33).

Since his focus includes the chronomes of the environment, with which those of life are intricately interwoven, Mendel, the chronobiologist, set yet another example by providing systematic data that allow the resolution of 1-year synchronized circannual and of other meteorological rhythms, once his data in meticulous handwriting are transformed into an electronic format. His legacy prompts findings discussed herein in their historical context. The multifrequency components of the chronomes in us are interwoven among themselves, with other chronome elements, and with chronomes around us, as feedsidewards par excellence, for the resolution of what can be regarded as a transdisciplinary "biggest problem".

Sequence within a circadian cycle: RNA before DNA

There is the chronobiologic question of what comes first in a single circadian (or other) cycle. Toward this goal, it seemed reasonable by the fifties to fill in the Gs (that stand for Gaps in knowledge) in the cell cycle of that time. These gaps remain exactly what the word means: it had to be realized that the cell cycle is a sequence of more than two events, such as DNA labelling and mitosis, and that referring to the rest as one of the Gs can be equivalent to building on quicksand (as if the gaps were more than lack of specific knowledge of what happens during a gap). For instance, the effects of agents such as pituitary growth hormone, GH (34), an ACTH analogue (35), or an immunomodulator (36), as already demonstrated, depend critically on a circadian, circaseptan or circannual cell cycle time and probably on many other as-yet not tested, e.g., circatrigintan, transannual rhythm stages, some of which are already mapped.

For replacing the Gs, in the 1950s we used a battery of techniques. For locating intracellular sites, we combined differential centrifugation and histology with wet chemistry and radioactive tracers. Physiological markers were the circulating blood eosinophils (gauging the adrenal cortex and medulla) and core temperature (as a marker of hypothalamic mechanisms underlying a mammalian circadian system). We determined the relative specific activities, i.e., the specific activity of chemically isolated phospholipid-, RNA- or DNA-phosphorus in relation to the specific activity of pool (acid soluble or inorganic) phosphorus. This approach yielded a biochemical sequence of events, starting with phospholipid labeling at the membrane, which preceded RNA formation in the cytoplasm. There was no need to obscure these features by reference to a gap, as G1. We dissected events in time further to find that RNA formation preceded the formation of DNA, rather than the reverse, with RNA preparing perhaps the cell for DNA synthesis and for the subsequent (again clearly following rather than coincident) division of the cell with an intermediate peak in glycogen content.

Thus, by the 1950s, what was to become chronobiology revealed that a circadian cell cycle in immature growing mouse liver starts at the membrane with phospholipid labeling. RNA-, not DNA-synthesis follows. With cosinor methodology for time series analysis, we could demonstrate a statistically significant lead in phase of phospholipid labelling over RNA formation. In mammalian liver, there is a lag of ~9 hours between RNA formation and DNA synthesis, with non-overlapping 95% confidence intervals, when the results are analyzed by cosinor. The results of the 1950s found extension by the 1960s. We learned from Leland Edmunds that the sequence of a peak in murine RNA formation (a result of synthesis) has a counterpart in RNA content, which leads that in DNA, in the unicell Euglena, within a single cell, not complicated by the presence of metabolizing cells that are not yet dividing (37). From there, it is just one further step to analyzing the sequence of gene expression in the mammalian heart (38).

The spectrum of ultradian rhythms broadens

The ultradian courtship song of the fruit fly is associated with circadian genetics (39), as may be developmental changes in the roundworm *Caenorhabditis elegans* (40). Ultradians and

infradians can replace circadians in the case of circulating endothelin (41-44) and in the numbers of endotheliocytes (45). Ultradians can also characterize gut hormones (46) and have been detected in molecular biology (47). Among non-photic infradian cycles in the environment, some long known counterparts of the ~10.5-year Schwabe and the ~21-year Hale cycles are now marked by signatures of the solar wind in the form of near-transyears (1.00 year < [τ {period} - CI {95% confidence interval}] < [τ + CI] < 1.20 years), far-transyears (1.2 years $\leq$ [τ - CI] < [τ + CI] < 1.9 years) and a cis-half-year found by Rieger (48), or an ~0.42-year cycle. Counterparts in physiology (49) must be aligned with those in pathology (50).

Circaseptans

An ~weekly or circaseptan pattern critically interacts with the outcome of an attempt to optimize, by timing, the effect of an immunomodulator in a mammal (36). In manipulating a unicell, the increasing interval in numbers of days between consecutive changes of an LD12:12 lighting regimen reveals an ~7-day pattern in the intact organism that changes to a half-weekly or circasemiseptan pattern after enucleation of the unicell (51). For the electrical potential of *Acetabularia* standardized in LD12:12 and released into continuous light, the circaseptan component is more prominent than the circadian. Both a circaseptan and a semicircaseptan pattern fit the declining vitality (gauged by the glutathione content) of the anucleate human platelet (52). Both these patterns fit data on growth or colony advance of E. coli (53).

A circaseptan pattern is apparent for cell settling in another unicell, *Euglena gracilis* Klebs; in the same unicell, *Euglena*, cell division also shows a circaseptan pattern (54). A mutation is associated with a change of this circaseptan pattern into a circasemiseptan one, in keeping with extremely limited yet further pertinent data (55). The multiseptans are just one set of harmonics of the sun's (solar latitude-dependent) rotation periods (56; cf. 57) and must be separated from periodicities associated with the moon. Among others, ~10- and ~5-day periods, described by G. Hildebrandt may also have been favored by an internal integrative evolution, complementing Darwinian adaptations.

The multiseptans may be linked to the circadian component, if, as seems to be the case in a hamster, a mutation involving a shortening of the circadian is associated with a circaseptan-to-circasemiseptan change of retinal melatonin production (insofar as curve-fitting to extremely short time series can allow speculation) (58).

The original documentation of the endogenicity of circaseptans was based originally on the monographic description of a case of human desynchronization from the societal week for ~3 years (59). It was strengthened by the observation that it related to only one variable -- 17-ketosteroid excretion, the breakdown product of some hormones -- and not to another variable, the urine volume, 7-day synchronized by a bottle of beer and an extra cup of tea each Sunday (59). The 17-ketosteroid also free-ran from the planetary geomagnetic index Kp and in records from hundreds of human newborns, showing a prominence of circaseptans, with amplitudes larger than those of the circadians in Brno, Moscow and Minneapolis.

There is a need for broader-than-circadian focus and the technology is available to implement it. Until this is done, however, short time series are valuable, as long as it has been made clear that inferences from data covering only one or a few putative cycles serve for hypothesis formulation and need added longitudinal or transverse validation in the same individual or across similar individuals, respectively. In the case of unicells, further experimental validation is required, with data inspection by the naked eye complemented with inferential curve-fitting. With these caveats, the chronobiology of unicells, just like that of arabidopsis, if not peas, and of mammals all add new dimensions to Mendel's legacy. One of these is the possible linkage of a built-in week and half-week in our chronomes to circadian and faster rhythms. The other related chronobiologic dimension is our resonance with events in the cosmos, which almost certainly has molded our genetic time structure. New components are being uncovered with periods of ~half a year, as in epileptic attacks (60) or in circulating melatonin of people living at high latitudes (61); of ~7 years, e.g., in marine invertebrates or in atmospheric pollution, or of ~10.5 and ~21 years, in neonatal morphology and adult physiology (62-64). These rhythms, found in biology, all have prominent counterparts in geomagnetic disturbance, responding to magnetic storms and other

events within and beyond the solar system, that need to be made amenable to concerted contemporaneous biomedical and purely physical measurement. Cis-half-years, transyears, decadals and multidecadals continue to be documented in this year's proceedings. Segregation and independent assortment are now known as laws of inheritance originating in Mendel's pea patch. In Siegelova's non-invasive cardiology "patch", the congruence of novel solar-terrestrial-biospheric periods and their independent assortment (selective congruence) await further study by chronomics.

Mendeliana

Against the foregoing chronobiologic background, we look back to the time some decades ago in Brno, when the centenary of the publication of Gregor Mendel's research with Pisum was marked by an international memorial symposium, and again to the time when under the ambitious title "The past, present and future of genetics" in Kuparovice, then Czechoslovakia, Mendel's role in the foundation and early development of genetics was reconsidered (65). To the wealth of memorabilia in these volumes and others, we add chrono-meta-analyses of some of Mendel's data in meteorology, Table 1.

Mendel measured wind speed in 16 directions in 1862 and summarized his data on a monthly basis. In 50% of the cases, a circannual component was the most prominent in the least squares spectrum spanning frequencies of 1 to 5 cycles per year. The circannual component is statistically significant in four cases ($P<0.05$) and is of borderline statistical significance in another two cases. As seen in Table 1, there seems to be a gradual change in the circannual acrophase of maximal wind speed as a function of the direction from which the wind blew: three clusters can be recognized, one from south to west-northwest with circannual acrophases occurring around September; one from northwest to east-northeast with acrophases occurring around May; and one from east to south-southeast, with acrophases occurring around December-January.

Hardly surprisingly, a circannual rhythm also characterizes environmental temperature ($P<0.001$). Mendel's data further allow the demonstration of an ~yearly rhythm in cloudiness ($P<0.001$) and rainfall ($P=0.004$), but not in atmospheric pressure ($P=0.411$). The largest positive

deviation in temperature is found in mid-July (acrophase = -205° from December 22, 1861, the latter date chosen as zero phase) in keeping with some rather high temperatures experienced whenever the senior author had the privilege of visiting Brno in mid-summer. The temperature acrophase corresponds to that of maximal rainfall (acrophase = -203°), whereas maximal cloudiness occurs in early January (acrophase = -15°). The predictable yearly changes in these variables can be quite large, those in temperature averaging 17.7° Reaumur.

Whether applied to data from physics or biology, computer methodology isolates and quantifies predictable features in serial data, that need not be regarded as "too complex". For chronobiologists, Mendel's finest legacy is his function as a role model for perseverance against the greatest of odds. In this context, Mendel provides solid advice, found in his handwriting, in a verse he took from Johann Wolfgang von Goethe, constituting Insert I (66; cf. 67).

One of us (AM) emphasizes Goethe's and Mendel's verse as her motto when describing Mendel's personality. We also owe her the reference to the painting that symbolizes Mendel's interests: a setting of a telescope, globe, compass needle, scrolls of maps, thermometer and pocket sundials. Some of the objects (telescope, thermometer, pocket sundials) were found among Mendel's relics. These artifacts symbolize Mendel's interest in meteorology. Perhaps, in view of his telescope, we may read into this legacy an interest by Mendel in a budding chrono-astrobiology far beyond earthly meteorology.

We owe Ivo Cetl the chronology of Mendel's scientific activities (65). Mendel published his studies on plant hybridization later than his findings in meteorology. His interest in the weather continued for much longer than any other of his concerns. Historians may indicate rightly that to establish a new science one needs no more than a good publication or two. The chronobiologic perspective we convey here is that Mendel's concerns in plant hybridization are interrelated with those in meteorology and apiculture. They should lead to more than local or terrestrial weather forecasting. We have an opportunity to benefit from space weather forecasting (68), perhaps to reduce traffic accidents, myocardial infarctions or strokes and epilepsy. On the basic side, we may also find in the cosmoi the origin for some of the now-genetically-anchored, heretofore neglected

components in the spectrum of biological rhythms, such as the ~5 and ~16-month and ~7-, ~10-, ~21-, ~35- and ~500-year cycles in nature, inanimate and animate (69-73), including those in ourselves (10, 49).

If the genetics of structure in time as well as in space have their origin in the resonance of organisms with the dynamics of the cosmoi, the "theological" week, regarded by too many as all culture and not nature (74), may have a physico-chemical basis (75). A computation of the oscillating frequency during the diffusion of ions in a magnetic field such as that of an organism shows values for a period of ~1 week (75). Accordingly, this presentation takes us from Mendel's interest in the weather over space weather forecasting to the origin of Mendel's "hard" genetics in the light of Darwin's "soft" genetics. At its start, life may have been a mere resonance with the chronomes in cosmoi near and far. Eventually, the environmental frequencies became anchored as chronomes in RNA and then in DNA-based systems, with some features of integration with our environs, "recapitulated" perhaps whenever a cell is born, in a cyclic fashion with choices among several time scales. The biological week and the ~5-month cycles as well as those of ~6 months, now built into us, still resonate with distant drummers, whether they originated as a response to the solar wind, to the moon and/or to even more remote stimuli. As we undertake the journey from rhythms to a budding chrono-astrobiology, we learn about new health effects that are both mirrored by our genetically anchored chronomes and still influenced by the environment.

Solar monitoring: where Gregor Mendel and Jarmila Siegelova meet

In his letter III to Carl Naegeli (76), dated November 6, 1867, Mendel wrote: "... I am no longer fit for botanical excursions, since the heavens have blessed me with an overweight which, in further parties on foot, notably in climbing hills, becomes too readily sensed as a consequence of general gravity" ("... auch tauge ich nicht mehr recht für botanische Excursionen, da mich der Himmel mit einem Uebergewichte gesegnet hat, welches sich bei weiteren Fusspartien, namentlich aber beim Bergsteigen, in Folge der allgemeinen Gravitation, sehr fühlbar macht.") Refraining from hiking, Mendel late in life made observations on sunspots. Iltis (77) reports the following notes that are the more noteworthy since the time of the observations, albeit a solar maximum was

not remarkable, Figures 5 and 6: "17 [November 17, 1882] vesp. aurora in Geneva and Pola; 18th, a.m., disturbance in telephone communications; 17th, 18th, aurora in San Francisco extending to Boston (very imposing!)." Iltis comments: "In [Mendel's] drawings of sunspots we find for the 18th and 19th of the same month a large group of spots near the central meridian of the sun's disk" (77). Thus, about 8 decades before Mariner 2 documented the solar wind, the scholar of heredity and of earthly weather looked for the link between solar activity and terrestrial affairs, Figures 5 and 6.

Herein lies the challenge of noninvasive cardiology, notably in Brno: to monitor both personal and societal health, the latter by solar surveillance via BP and HR across generations, to map the spectral region between BEL cycles of ~35 years and Mikulecky's circasemimillennials. We may become able to do so with modern instrumentation developed by the Phoenix Study Group, composed of volunteering members of the Twin Cities chapter of the Institute of Electrical and Electronics Engineers (http://www.phoenix.tc-ieee.org). An unobtrusive and affordable software and hardware combination with modern computer technology is an important step toward universal preventive cardiac health care, so that as long as health prevails, all is being done by cost-free self-help, as practiced now in BIOCOS, and we contribute concomitantly to what is today basic science, but tomorrow may lead to countermeasures against ills of society, influenced unfavorably by solar activity.

Support: GM-13981 (FH), University of Minnesota Supercomputing Institute (GC, FH), MSM0021622402

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Legends

Figure 1. Measurable time structure (chronome) of a variable. More and more components in the spectrum of physiological variation are found to have numerical physical environmental counterparts and, vice versa, environmental counterparts have been found for some unusual physiological cycles, believed to be purely societal, such as the week, and for new cycles shorter than 6 months and longer than 12 months, signatures of the solar wind. Physical or biological spectra, organizing irregular chaotic and complex variations and trends in endpoints of rhythms, chaos, and complexity constitute time structures, or chronomes. The mapping of physical and biological chronomes proceeds as yet opportunistically in a project on The BIOsphere and the COSmos (BIOCOS). A data base of reference values thus accumulates with a target length of at least 7 days beat-to-beat for the electrocardiogram and again for at least 7 days at intervals from 15-60 minutes, in the case of human blood pressure. Such mapping is critical for a quantification of health in the range of otherwise neglected physiological variation. Chronome maps are the invaluable and indispensable reference values for the detection of disease risk syndromes. "Measure what is measurable and render meaningfully measurable in time what as yet is not" is what chronomes are all about. © Halberg.

Figure 2. Sketch of factors and pathways known to participate in frequency synchronization *among* circadian rhythms themselves, as well as in synchronization between rhythm(s) and environmental synchronizer(s). Note intracellular mechanisms documented by 1960 (5-7). © Halberg.

Figure 3. **Left**: Chronomodulation at different levels: in the **left** half, interplanetary solar and galactic factors (**top right**) are conceived as modulating socioecological conditions in the habitat (**top left**), acting upon the healthy or sick organism as a whole. **Right**: Results on lack of effect, attenuation, or amplification by aqueous pineal homogenate of corticosterone production by bisected adrenals are summarized on top. Those in the second diagram from the top refer to the effect of the bilateral ablation of the suprachiasmatic nuclei (SCN) on circadian amplitude and acrophase. Loss of circadian rhythm (documented by a zero amplitude) is the result of SCN

removal in the case of locomotor activity and water drinking but not in a vast majority of other rhythms sampled at 4-hour or shorter intervals for 24 hours or longer spans and analyzed by inferential statistical means. The third diagram from the top refers to chronomodulation by feedsidewards observed for the effect of ACTH 1-17 upon metaphysical DNA labeling in the rat. Intermodulations in the case of an invading microorganism of sufficient virulence to elicit a host response are sketched at the bottom. Feedsideward: Multiple interactions among several rhythmic entities resulting in a predictable rhythmic sequence of attenuation, no effect, and amplification, implemented by a modulator acting on the interaction between the actor and reactor. As shown in the diagrams, the role played by the modulator, the actor, and the reactor can vary among the interacting entities, and these systems can be exposed to different influences and an integrator.

- actor ↔ reactor;
- modulator ↔ actor;
- modulator ↔ reactor;
- feedsideward;
- integrator;
- → influencers.

© Halberg.

Figure 4. The chronomes in us, that came about as a function of chronomes around us, to be eventually coded genetically, await further exploration in health care, notably for stroke prevention. © Halberg.

Figure 5. On November 17, 1882, Mendel made the connection between sunspots and the aurora during a solar maximum that was not unusual whether it is viewed in the context of centuries (top), that of years (second row), of months (third row) or of days (bottom row). © Halberg.

Figure 6. Mendel's drawings of sunspots show almost-daily changes in their appearance; sometimes the sun's disk is free of spots. These observations led him to postulate a connection between sunspots and the aurora. From (60).

Insert I: Mendel's citation (from Goethe's "Lila" [66]) is pertinent to the switch (from the fictions of homeostasis, secularity, baselines and other current dogmas) to chronobiology

Feiger Gedanken,	(Cowardly thoughts,
Bängliches Schwanken,	anxious vacillation,
Weibisches Zagen,	spineless* hesitation,
Ängstliches Klagen,	anguished complaint,
Wendet kein Elend,	does not alleviate misery,
Mach dich nicht frei.	does not set you free.
Allen Gewalten	Opposing all force
Zum Trutz sich erhalten,	while maintaining one's course,
Nimmer sich beugen,	never to bend,
Kräftig sich zeigen ...	to show oneself strong ...)

*Goethe's "weibisches" literally translates as "woman-like", connoting "effeminate". We here change this reference into a gender-neutral one on the assumption that hesitation is not specific to a supposedly "weaker sex", as documented by women warriors (67).

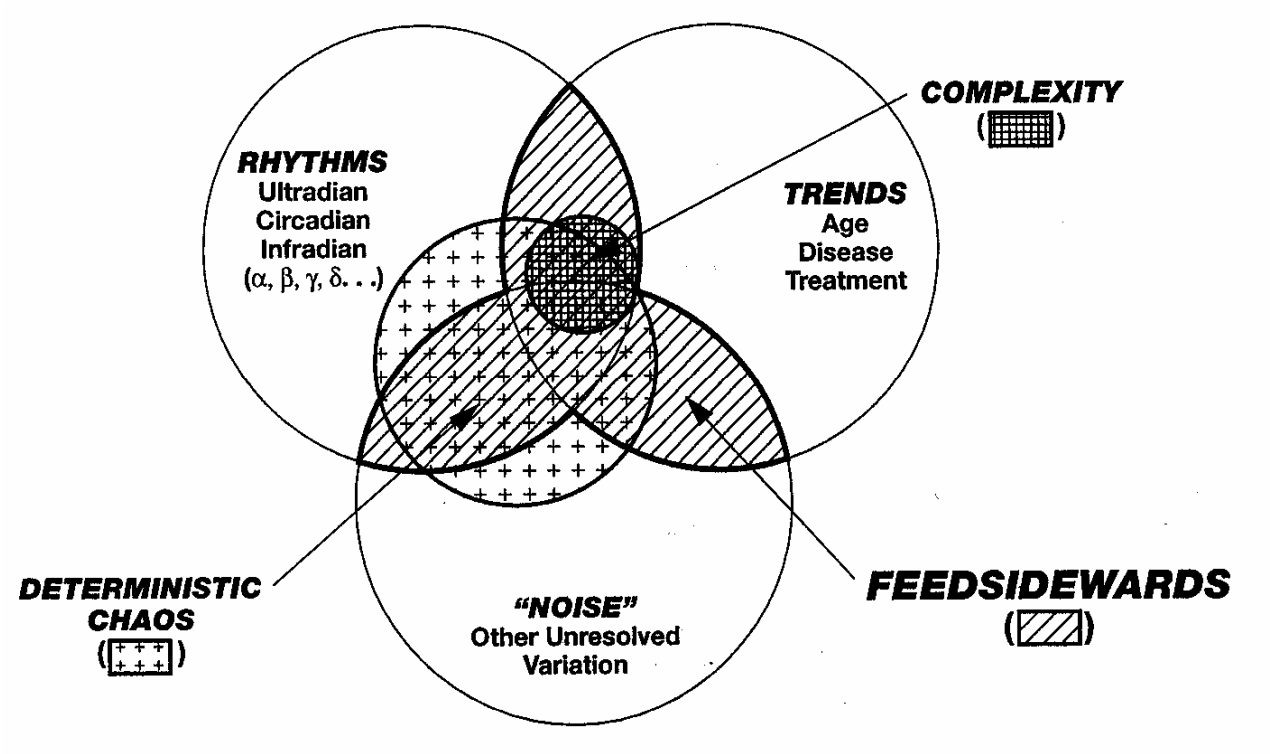

COMPLEXITY
RHYTHMS
Ultradian
Circadian
Infradian
(α, β, γ, δ. . .)
TRENDS
Age
Disease
Treatment
DETERMINISTIC
CHAOS
"NOISE"
Other Unresolved
Variation
FEEDSIDEWARDS

Figure 1

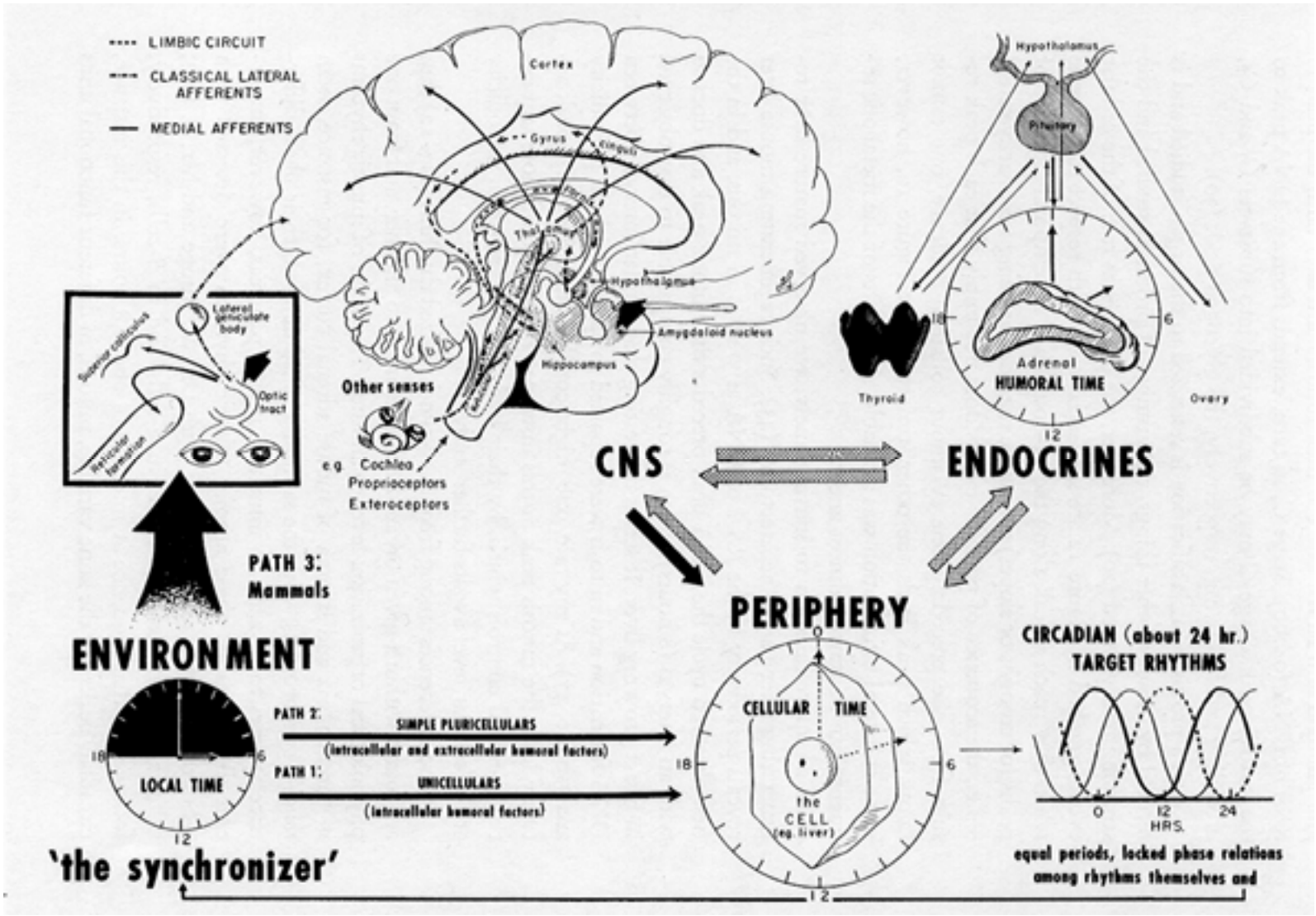
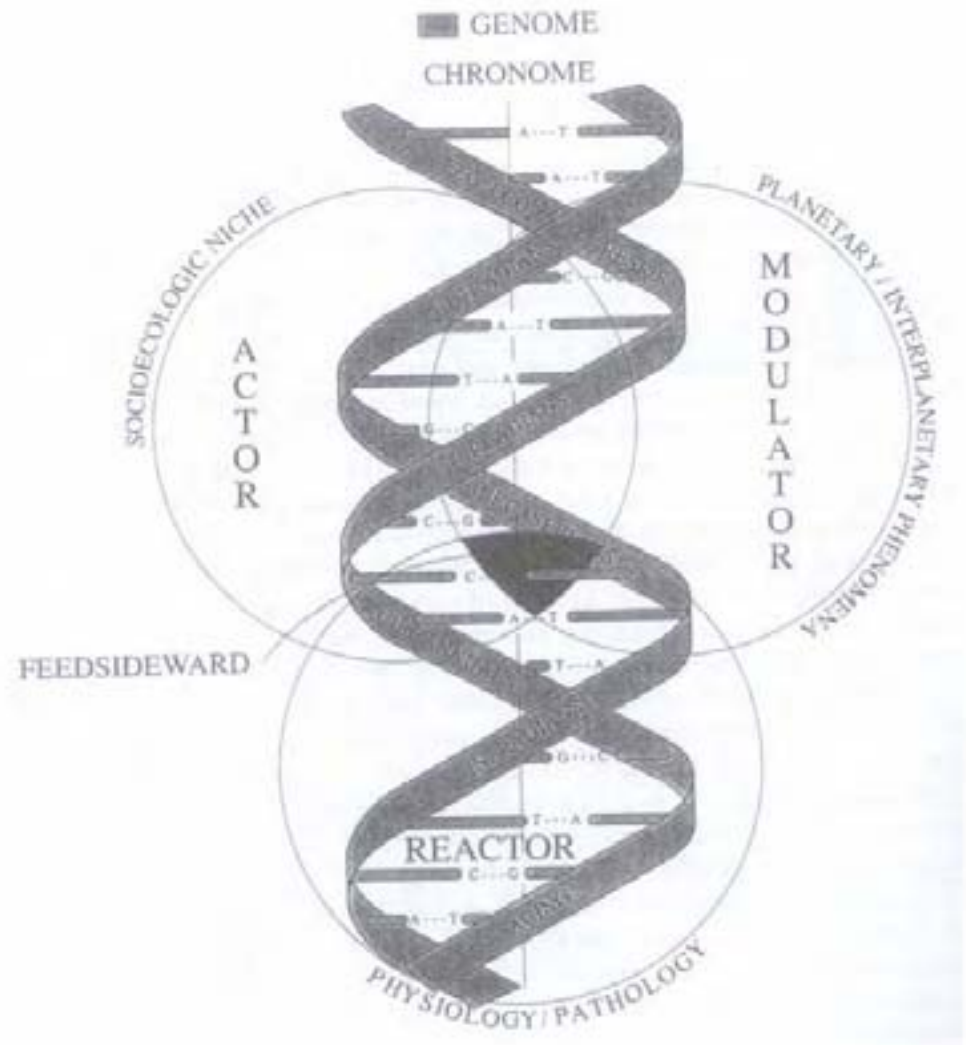

LIMBIC CIRCUIT
CLASSICAL LATERAL AFFERENTS
MEDIAL AFFERENTS
Cortex
Gyrus
Cingulum
Thalamus
Hypothalamus
Amygdaloid nucleus
Hippocampus
Other senses
e.g. Cochlea
Proprioceptors
Exteroceptors
Lateral geniculate body
Superior colliculus
Optic tract
Reticular formation
PATH 3:
Mammals
ENVIRONMENT
CNS
ENDOCRINES
Hypothalamus
Pituitary
Thyroid
Adrenal
HUMORAL TIME
Ovary
PERIPHERY
CELLULAR TIME
the CELL
(eg. liver)
LOCAL TIME
PATH 2:
SIMPLE PLURICELLULARS
(intracellular and extracellular humoral factors)
PATH 1:
UNICELLULARS
(intracellular humoral factors)
'the synchronizer'
CIRCADIAN (about 24 hr.)
TARGET RHYTHMS
HRS.
equal periods, locked phase relations
among rhythms themselves and

Figure 2


GENOME
CHRONOME
SOCIOECOLOGIC NICHE
PLANETARY / INTERPLANETARY PHENOMENA
ACTOR
MODULATOR
FEEDSIDEWARD
REACTOR
PHYSIOLOGY / PATHOLOGY

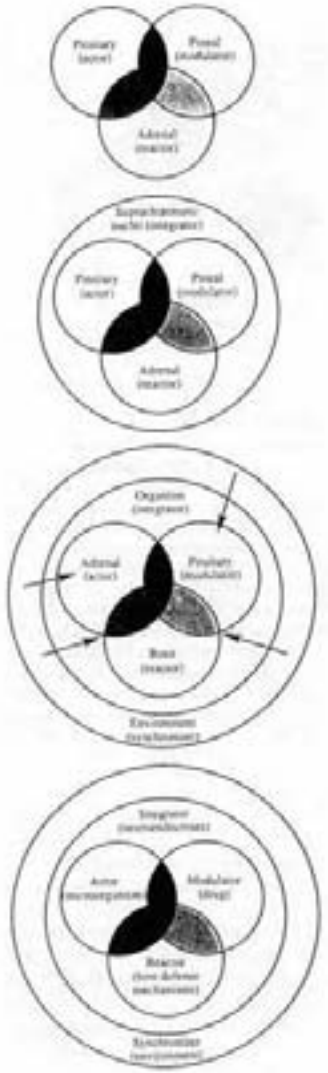


Figure 3

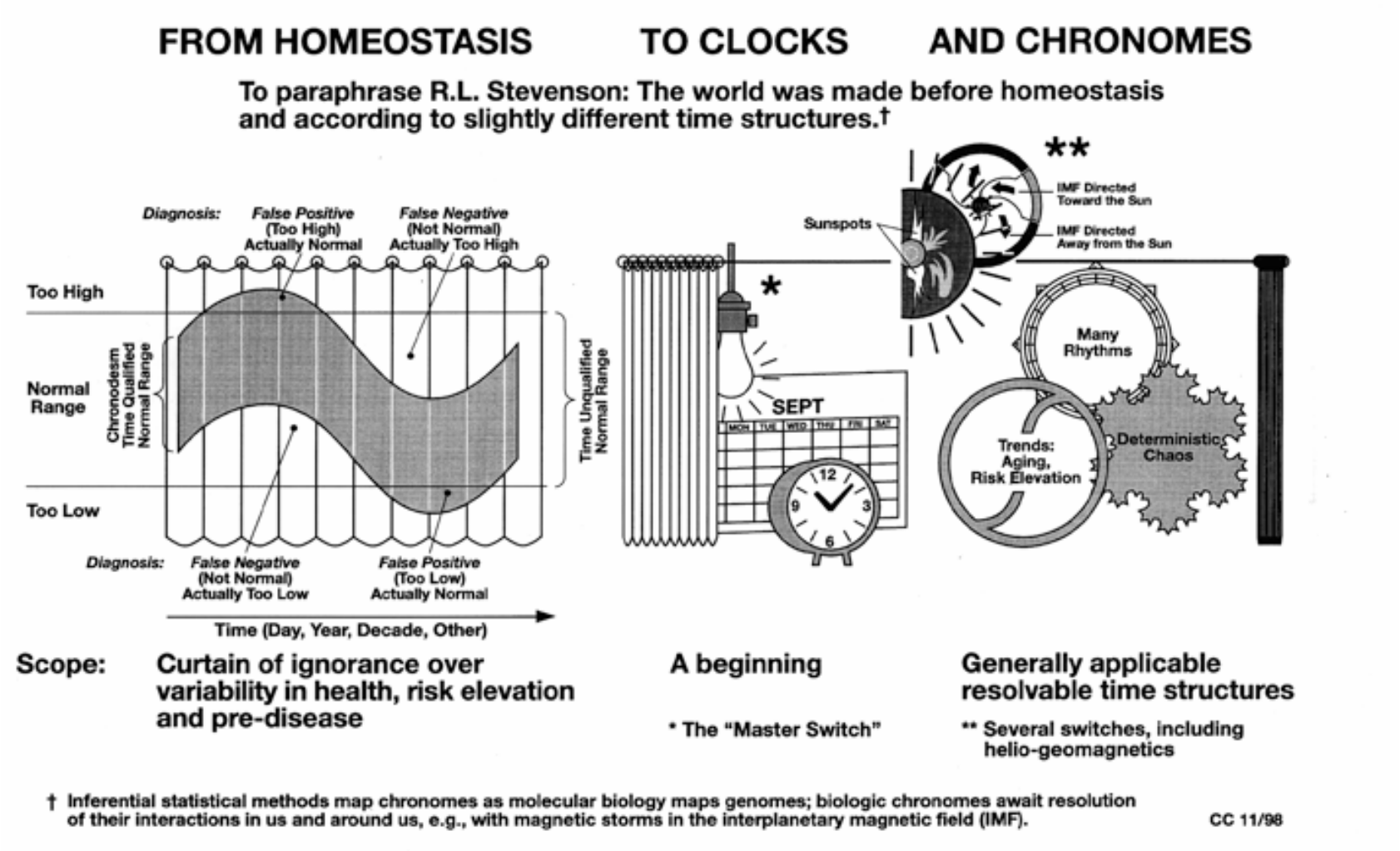

FROM HOMEOSTASIS TO CLOCKS AND CHRONOMES
To paraphrase R.L. Stevenson: The world was made before homeostasis and according to slightly different time structures.†
Diagnosis: False Positive (Too High) Actually Normal
False Negative (Not Normal) Actually Too High
Too High
Normal Range
Too Low
Chronodesm Time Qualified Normal Range
Time Unqualified Normal Range
Diagnosis: False Negative (Not Normal) Actually Too Low
False Positive (Too Low) Actually Normal
Time (Day, Year, Decade, Other)
Sunspots
IMF Directed Toward the Sun
IMF Directed Away from the Sun
SEPT
Many Rhythms
Trends: Aging, Risk Elevation
Deterministic Chaos
Scope:
Curtain of ignorance over variability in health, risk elevation and pre-disease
A beginning
* The "Master Switch"
Generally applicable resolvable time structures
** Several switches, including helio-geomagnetics
† Inferential statistical methods map chronomes as molecular biology maps genomes; biologic chronomes await resolution of their interactions in us and around us, e.g., with magnetic storms in the interplanetary magnetic field (IMF).
CC 11/98

Figure 4

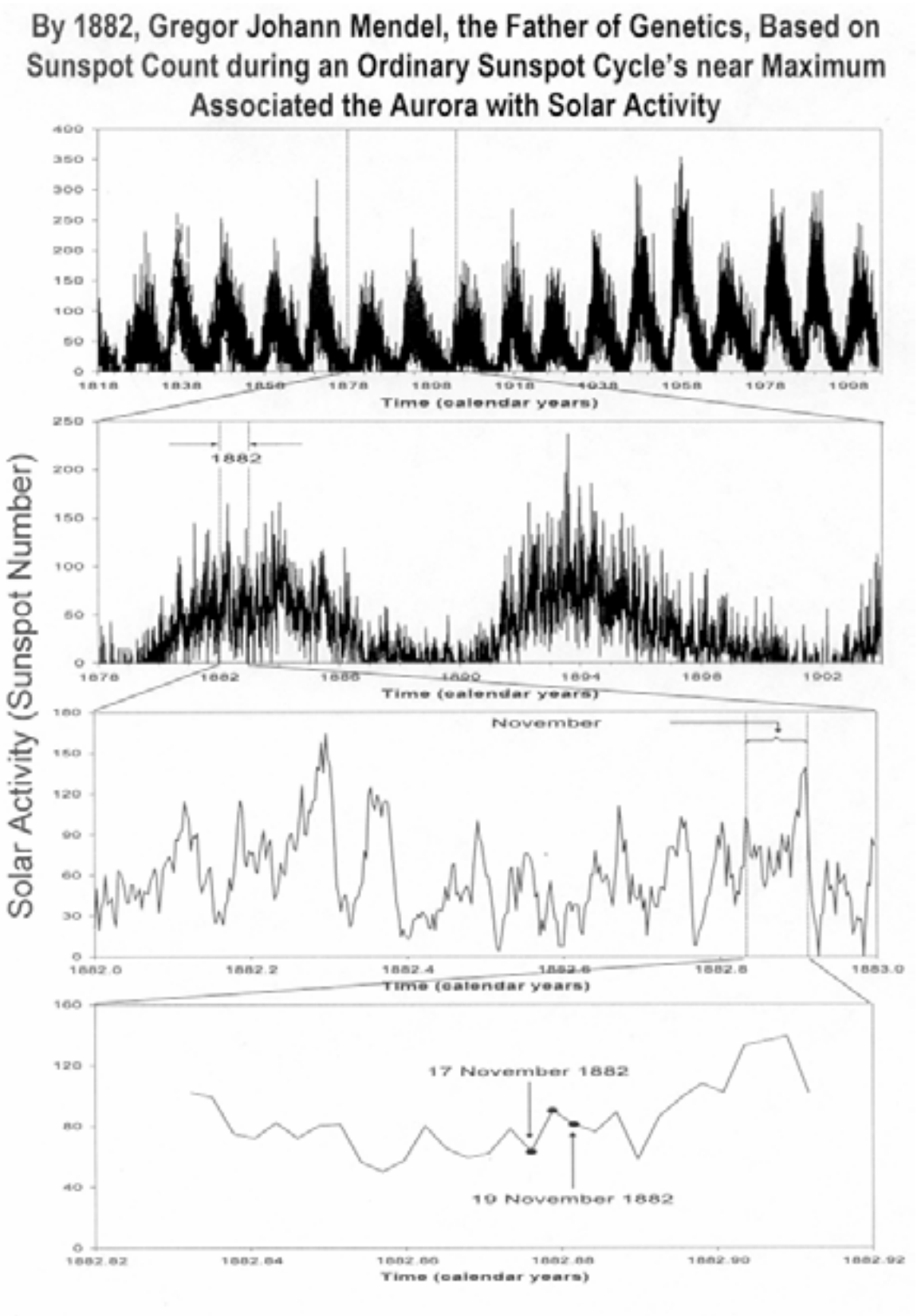
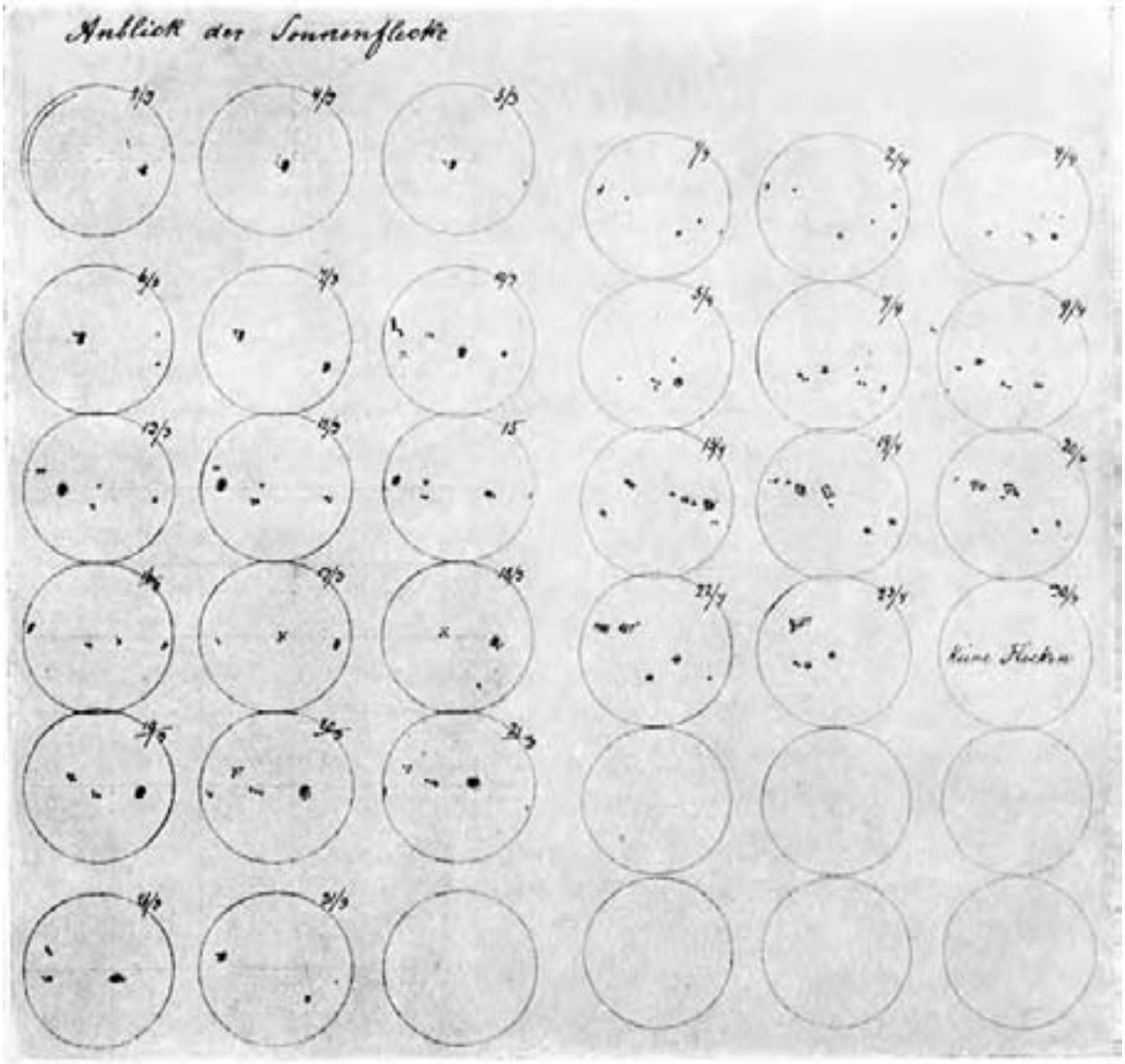

By 1882, Gregor Johann Mendel, the Father of Genetics, Based on Sunspot Count during an Ordinary Sunspot Cycle's near Maximum Associated the Aurora with Solar Activity
Solar Activity (Sunspot Number)
Time (calendar years)
1882
November
17 November 1882
19 November 1882

Figure 5

Mendel's notebook records date, number and location of sunspots, if any*



*View of sunspots *(Anblick der Sonnenflecke)* or of their lack (empty circles; *Keine Flecken)* in two pages with Mendel's sketches (from Iltis H. Life of Mendel. New York: Hafner, 1966 [originally published in English in 1932]. 336 p.)

Figure 6

Table 1: **BOLD** WHEN STATISTICALLY SIGNIFICANT CIRCANNUAL VARIATION OF WIND SPEED IN GREGOR MENDEL's HANDWRITTEN RECORDS (1862)*

Results from single cosinor

Direction	PR	P	MESOR±SE	Double Amplitude	Acrophase±SE
Cluster 1					
s	2	0.899	8.5±0.7	0.90±1.92	-292±124
ssw	46	0.063	1.7±0.2	1.62±0.58	-299±21
sw	12	0.550	1.5±0.2	0.64±0.58	-248±51
wsw	25	0.270	1.3±0.2	0.88±0.50	-252±33
w	10	**0.004**	6.9±0.3	3.28±0.70	-295±12
wnw	52	**0.038**	5.2±0.2	2.16±0.70	-257±18
Cluster 2					
nw	36	0.137	15.4±0.9	5.42±2.42	-174±26
nnw	45	0.067	8.0±0.5	4.18±1.54	-142±21
n	30	0.206	12.5±0.7	3.80±1.96	-167±29
nne	34	0.156	2.3±0.2	1.36±0.64	-148±27
ne	7	0.735	2.5±0.4	0.82±1.02	-170±72
ene	18	0.408	2.1±0.1	0.34±0.24	-113±41
Cluster 3					
e	10	0.627	6.3±0.4	1.22±1.24	-36±58
ese	20	0.367	2.4±0.2	0.96±0.64	-28±38
se	65	**0.009**	8.3±0.5	5.62±1.38	-17±14
sse	71	**0.004**	6.3±0.4	4.80±1.02	-348±12

Results from population-mean cosinor

Cluster	PR	P	MESOR±SE	Amplitude (% MESOR) (95% CI)	Acrophase (95% CI)
1	34.5	**0.030**	4.2±1.5	23.55 (9.72, 37.39)	-275˚ (-232, -302)
2	28.3	**0.023**	7.1±3.0	18.12 (9.12, 27.12)	-154˚ (-137, -175)
3	41.5	0.116	5.8±1.9	24.04 ( )	-10˚ ( )

*s: south; w: west; n:north; e: east. PR=percent rhythm; P=P-value from test of zero-amplitude (no-rhythm) hypothesis; SE=standard error; 95% CI=95% confidence interval. Units in original handwritten record not readily legible. When all amplitudes are set equal to 1 to summarize acrophases only, a circannual component is statistically significant in all 3 clusters (P≤0.001). Biological significance of record is historical, showing the environmental concern of the founder of genetics.